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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,631	02/19/2002	Paul Habermann	DEAV2001/0007USNP	2601

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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
10/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/076,631	HABERMANN, PAUL	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-12 and 27-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-12 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 25, 2008 has been entered. Claim 1 has been amended. Claims 2-5 and 13-26 have been canceled. Claims 30-37 have been added. Accordingly, claims 1, 6-12 and 27-37 are examined herewith to the extent that the claims read on the elected invention. As discussed in Applicant's response to a restriction requirement on September 29, 2005, regarding the variables recited in the claims, P is the ADH2 promoter, S is the yeast alpha mating factor leader sequence, B is a chemical bond, Z1 is a codon for K, Z2 is a codon for R and T is a 3' interleukin-2 sequence.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

Claims 30-37 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 1 and 6-12. Claims 27-29 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 8, 11 and 12. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 30-37 are drawn to an article of manufacture,

while claims 1 and 6-12 are drawn to a polynucleotide, but there appears to be no difference between the two. The two polynucleotides are identical. Thus, the claims are duplicates. Claims 8, 11 and 12 are drawn to a host cell, while claims 27-29 are drawn to an engineered host cell. But, the two host cells are identical, and the term host cell entails the expression of (or at least the carrying of) an exogenous vector construct that is engineered. Thus, the claims are duplicates. Appropriate correction is required. Duplicate claims should be either amended so that they are different in scope from the first claims or canceled.

Claim Rejections - 35 USC § 112, first paragraph

In view of Applicant's amendments to the claims, the written description rejection in the previous Office action is withdrawn and replaced with the following rejection.

Claims 1, 6-12 and 27-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the claims recite the genera of a hirudin variant and of T, an untranslated expression-enhancing polynucleotide that is located 3' to the pro-insulin sequence in the claimed polynucleotide. Regarding hirudin variants, the specification discloses no hirudin variants but states that a hirudin variant in the claimed invention may have an unlimited number of any type of substitutions and/or deletions and/or additions (see p. 8). The specification also discloses that naturally occurring hirudin isoforms may be used in the claimed invention. As the naturally occurring isoforms are known in the art, polynucleotides encoding the naturally occurring isoforms would be considered to meet the written description requirement. But, polynucleotides encoding undisclosed variants do not. Regarding T, while termination or

terminator sequences that enhance gene expression are known and conventionally used in the art, Applicant's genus of T is broader than termination/terminator sequences, as T is anything that enhances expression and is not translated. No specific T's are disclosed in the specification. As a result, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera. A sufficient written description of a genus of polynucleotides (or their encoded polypeptides) may be achieved by a recitation of structural features common to each member (species) of the genus, **which features constitute a substantial portion of each member of the genus**. The only recited features of the genera in these claims are functional limitations (encoding a hirudin variant and enhancing expression), which do not constitute a substantial portion of each species in these genera, as the structures of the claimed species are completely undefined and the specification does not define the structural features necessary for members of these two genera to be selected. Therefore, one skilled in the art cannot reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

Consequently, there is no evidence that a sufficient number of representative species of these large genera were in the possession of the inventors at the time of filing. To satisfy the written description aspect of 35 U.S.C. 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Because no species of the genus T are disclosed, and because the only hirudin variants disclosed are the naturally occurring isoforms, the claims fail to satisfy the written description requirement.

In view of Applicant's amendments to the claims, the written description rejection in the previous Office action is withdrawn and replaced with the following rejection.

Claims 1, 6-12 and 27-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hirudin or naturally occurring isoforms thereof, and while being enabling for a T that is a termination sequence or terminator sequence, does not reasonably provide enablement for any variant of hirudin or a T that is anything that is not translated and that enhances gene expression. Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether or not undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the relative skill of those in the art, (5) the predictability or unpredictability of the art, (6) the amount or direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary. Although the quantity of experimentation alone is

not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

Factors pertinent to this discussion include the predictability of the art, guidance in the specification, the breadth of claims and the amount of experimentation that would be necessary to use the invention.

Regarding hirudin variants, while recombinant and mutagenesis techniques are known, it is not routine in the art to screen for vast numbers of multiple substitutions and/or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein, the result of which is

unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, *e.g.* multiple substitutions. The claims encompass polynucleotides encoding hirudin variants having any number of mutations of any type. Thus, the number of mutations in any of a vast number of combinations (substitutions and/or deletions and/or insertions) encompassed by the claims is extremely large.

The specification does not support the broad scope of the claims which encompass a polynucleotide encoding any hirudin variant, because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting hirudin activity (anticoagulant activity or membrane-transport activity), including the amino acid positions that make up the catalytic or substrate binding or receptor binding site; (B) the general tolerance of hirudins to modification and the extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices are likely to be successful.

Without sufficient guidance, which has not been provided (beyond the statement that one may use naturally occurring isoforms), obtaining a hirudin variant that is a functional equivalent of a naturally occurring hirudin for use in the claimed polynucleotide is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a polynucleotide encoding any hirudin variant. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

Regarding the genus of T's, polynucleotides that enhance gene expression and are untranslated, the specification does not support the broad scope of the claims which encompass any T, because the specification does **not** establish which types of polynucleotides other than termination/terminator sequences may be used in the claimed invention. For example, may a second promoter or an enhancer or a second secretion signal be used as T? Because these types of polynucleotides are not disclosed, specific examples of each of these types are also not disclosed. The specification does not disclose a rational and predictable scheme for identifying these additional types of polynucleotides. Thus, the specification provides insufficient guidance as to which of these other types of polynucleotides are likely to be successful when used in the claimed invention.

Without sufficient guidance, which has not been provided, obtaining a T that may successfully be used in the claimed polynucleotide is unpredictable, and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. One of skill in the art would have to experiment unduly on a random make-and-test-for-function basis to identify polynucleotides that may be used as T. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any T. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

In view of the foregoing, the claims fail to satisfy the enablement requirement.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-12 and 27-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Although the claims have been searched and examined in accordance with the elected species for Z1 and Z2, codons encoding K and R, Applicant should be aware of the following points with respect to putting the claims in condition for allowance. The limitations recited in claims 1 and 30 are ambiguous, confusing and, in part, lack antecedent basis, rendering the meaning and the scope of the claims indefinite. One of the "wherein" clauses recites that Z1 and/or Z2 is a chemical bond when Z1 and Z2 combine to make the second Z1Z2, but it cannot be understood what a second Z1Z2 is. The meaning of this claim limitation cannot be understood. Also, claims 1 and 30 recite the limitation "m=0." There is insufficient antecedent basis for this limitation in the claims, as the generic and variable polynucleotide does not have an m. Clarification and appropriate correction are required.

Further, it is confusing as to how Z1 and Z2 can be partial codons. If Z1 and/or Z2 are partial codons, the total number of nucleotides will be a number between 1 and 5. 1, 2, 4 or 5 nucleotides means that the proinsulin sequence is out of frame, and a fusion peptide containing proinsulin is not encoded. 3 nucleotides means that an amino acid other than K or R is encoded, such as N or S (e.g., codons such as aac, aat, agc and agt are present). Such constructs would be inoperative for producing proinsulin .

Applicant may correct the claims by amending them to recite simply that Z1 is a codon for K or a codon for R or absent, *idem* for Z2.

Claim Rejections - 35 USC § 101

Upon reconsideration of the claims, this rejection is withdrawn.

Claim Rejections - 35 USC § 102

In view of Applicant's amendments to the claims, this rejection is withdrawn.

Double Patenting- Obviousness-type

As discussed in the previous Office actions, claims 1, 6-12 and 27-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 5 and 9-13 of copending Application No. 10/076,634 (published as US 2003/0044906 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is drawn to the same polynucleotide. The comprising language of copending claim 1 does not exclude the promoter, secretion signal and termination signal recited in instant claim 1, and because these elements are conventional in the art, it would have been obvious to one of ordinary skill in the art at the time of the invention to add them to improve gene expression. The copending claims are broader, because the Asm variable (Z1 in the instant claims) can be 0 – 10 codons, while instant Z1 is 0 – 1 codons (or a fraction of a codon that makes a codon with Z2- as discussed above, the claim language is confusing). Nevertheless, the two polynucleotides are not patentably distinct. Also, the copending claims recite different recombinant host cells (bacterial) than the instant claims (yeast), but each host cell, whether bacterial or yeast, is one that is conventionally used in the art. The point of novelty does not lie in the host cell.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant notes in his response that this rejection will be addressed at a later date "when claims are finalized by indication of allowable claimed subject matter." In reply, this rejection is

still outstanding and must be addressed. Until this rejection is overcome, the claims cannot be "finalized." Appropriate correction is required.

Similarly, claims 1, 6-12 and 27-37 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-13 and 31-35 of copending Application No. 10/076,632 (published as US 2003/0176673 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is drawn to the same polynucleotide. The copending claims are broader, because the Asm variable (Z1 in the instant claims) can be 0 – 10 codons, while instant Z1 is 0 – 1 codons (or a fraction of a codon that makes a codon with Z2- as discussed above, the claim language is confusing). Nevertheless, the two polynucleotides are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Also similarly, claims 1, 6-12 and 27-37 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 4-10 of U.S. Patent No. 7,202,059. Although the conflicting claims are not identical, they are not patentably distinct from each other because each set of claims is drawn to the same polynucleotide. The comprising language of copending claim 1 does not exclude the promoter, secretion signal and termination signal recited in instant claim 1, and because these elements are conventional in the art, it would have been obvious to one of ordinary skill in the art at the time of the invention to add them to improve gene expression. The patented claims are broader, because the Asm variable (Z1 in the instant claims) can be 0 – 10 codons, while instant Z1 is 0 – 1 codons (or a fraction of a codon that makes a codon with Z2- as discussed above, the claim language is confusing). Nevertheless, the two polynucleotides are not patentably distinct. Also, the

patented claims recite different recombinant host cells (bacterial) than the instant claims (yeast), but each host cell, whether bacterial or yeast, is one that is conventionally used in the art. The point of novelty does not lie in the host cell. Therefore, the two claim sets are not patentably distinct.

Examiner has made an earnest attempt to identify patents and patent applications for the purpose of rejecting claims that raise the question of double patenting. It is noted, however, that numerous co-pending applications have been filed and continue to be filed, and patents have issued and continue to issue disclosing subject matter that is related to the instant application. In the interest of compact prosecution, Examiner requests that: 1) Applicant identify any patent(s) and/or co-pending application(s) that claim(s) subject matter that may necessitate a double patenting rejection, an obviousness-type double patenting rejection, a provisional double patenting rejection, or a provisional obviousness-type double patenting rejection; 2) identify the claims of the patents and/or co-pending applications that claim identical or similar subject matter; 3) identify the corresponding claims of the instant application, and 4) take the appropriate action, e.g., cancel claims to preempt a statutory double patenting rejection and/or file a terminal disclaimer to preempt an obvious-type double patenting rejection or provisional rejection. Applicant's cooperation in following steps 1) to 4) above is appreciated as this will allow the examiner to focus on more substantive issues in the examination of the instant application.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rosanne Kosson
Examiner, Art Unit 1652
rk/2008-10-10

/Rebecca E. Prouty/
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